Image AF/1647

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December 17, 2003

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Mail Stop Appeal Brief - Patents
Art Unit 1647

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Re: U.S. Utility Patent Application
Appl. No. 09/380,704; § 371 Date: June 6, 2000
For: **A Composition Comprising a Metal Chelator and a Method of Treating Amyloidosis by Administering the Metal Chelator**
Inventors: Bush *et al.*
Our Ref: 0609.4350001/JAG/FRC

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Fee Transmittal Form (PTO/SB/17);

2. Brief on Appeal Under 37 C.F.R. § 1.192 (in triplicate) along with Exhibits 1-7;

3. Form PTO-2038 Credit Card Payment Form in the amount of **$165.00** to cover the Brief filing fee; and

4. Return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Frank R. Cottingham
Attorney for Appellants
Registration No. 50,437

FRC/pcd
Enclosures

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PTO/SB/17 (08-03)
Approved for use through 07/31/2006. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($)165.00

Complete if Known	
Application Number	09/380,704
§ 371 Date	June 6, 2000
First Named Inventor	Bush *t al.*
Examiner Name	Bunn r, B.
Art Unit	1647
Attorney Docket No.	0609.4350001/JAG/FRC

METHOD OF PAYMENT (check all that apply)

☐ Check ☒ Credit card ☐ Money Order ☒ Other** ☐ None

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☐ Deposit Account
Deposit Account Number 19-0036
Deposit Account Name: Sterne, Kessler, Goldstein & Fox P.L.L.C.

The Commissioner is authorized to: (*check all that apply*)

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☒ Charge any additional fee(s) during the pendency of this application

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1105	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) _____

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra	Fee from below	Fee Paid
Total Claims _____ - 20** =	_____	X _____	= _____
Indep. Claims _____ - 3** =	_____	X _____	= _____
Multiple Dependent	_____		= _____

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	**Reissue independent claims over original patent
1205	18	2205	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)_____

***or number previously paid, if greater; For Reissue, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1502	50	2052	25	Surcharge-late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	**330**	**2402**	**165**	**Filing a brief in support of an appeal**	**165.00**
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)165.00

SUBMITTED BY

Complete *(if applicable)*

Name (Print/Type)	Frank R. Cottingham	*Registration No. (Attorney/Agent)*	50,437	*Telephone*	202-371-2600
Signature	Frank R. Cottingham			*Date*	DEC. 17, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2953
BUSH *et al.*	Art Unit: 1647
Appl. No. 09/380,704	Examiner: Bunner, B.
§ 371 Date: June 6, 2000	Atty. Docket: 0609.4350001/JAG/FRC
For: **A Composition Comprising a Metal Chelator and a Method of Treating Amyloidosis by Administering the Metal Chelator**	

Brief on Appeal Under 37 C.F.R. § 1.192

Mail Stop Appeal Brief - Patents

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

A Notice of Appeal from the final rejection of claims 1, 2 and 37 was filed on October 17, 2003. Appellants hereby file this Appeal Brief in triplicate, together with the required brief filing fee.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

I. Real Parties in Interest (37 C.F.R. § 1.192(c)(1))

The real parties in interest in this appeal are The General Hospital Corporation and Prana Biotechnology Limited.

II. Related Appeals and Interferences (37 C.F.R. § 1.192(c)(2))

Appellants' undersigned representative is not aware of any appeals or interferences related to the captioned application.

III. Status of Claims (37 C.F.R. § 1.192(c)(3))

The captioned application was filed under 35 U.S.C. § 371 on September 8, 1999 and is a U.S. national phase application of international application No. PCT/US98/04683, filed on March 11, 1998. As originally filed, the application contained a total of 94 claims.

In a Preliminary Amendment filed on May 17, 2002, claims 3-36, 39-52 and 54-94 were cancelled, and claims 1 and 37 were amended.

In an Amendment filed on February 26, 2003, claims 1, 2, 37, 38 and 53 were amended.

In an Amendment filed on October 17, 2003, claim 38 was cancelled and claims 1 and 37 were amended.

Claims 1, 2, 37 and 53 are pending in the application.

Claim 53 is allowed.

Claims 1, 2 and 37 are now on appeal. A copy of the claims on appeal can be found in the attached Appendix.

IV. Status of Amendments (37 C.F.R. § 1.192(c)(4))

All amendments have been entered. No amendments have been filed subsequent to the issuance of the final Office Action dated May 22, 2003.

V. Summary of Invention (37 C.F.R. § 1.192(c)(5))

Amyloidosis is a general term which refers to any disease characterized by the extracellular accumulation of amyloid beta (Aβ) in organs and tissues. *See* Specification at page 24, lines 15-16. For example, Aβ deposits in the brain are believed to be responsible for the neuronal defects that lead to Alzheimer's disease. Aβ deposits are concentrated in regions of neuronal cell death in the brains of Alzheimer's disease patients. *See* Specification at page 1, lines 16-25. In addition, polymers of Aβ are neurotoxic to neurons in culture. *See* Specification at page 2, lines 11-25. Aβ-mediated neurotoxicity may be the result of the production of reactive oxygen species (ROS) such as hydroxyl radical (OH•), superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2). *See* Specification at page 41, line 13 through page 42, line 4. Since Aβ deposits are believed to be the cause of the tissue toxicity that is associated with amyloidosis, agents that interfere with and/or reverse Aβ deposition are sought after to treat amyloidosis.

The regulation of zinc and copper is abnormal in the brains of Alzheimer's disease patients. It has been found that zinc and copper are integral components of Aβ deposits. *See* Specification at page 90, line 23, through page 91, line 4. Experiments have shown that Aβ deposition is mediated by the presence of Zn^{2+} and Cu^{2+} ions. *See* Specification at page 3, lines 5-10. For example, Zn^{2+} and Cu^{2+} dramatically induce the precipitation of Aβ *in vitro*. *See* Specification at page 53, line 24, through page 54, line 14. The present inventors have

shown that metal chelators (*i.e.*, agents that reduce the amount of free metal ions) inhibit Aβ deposit formation and solubilize Aβ aggregates. *See, e.g.*, Specification at page 90, line 12 through page 97, line 14 (Example 5). Bathocuproine is an exemplary metal chelator. Bathocuproine was found by the inventors to solubilize Aβ deposits and interfere significantly with copper-mediated generation of Aβ polymers. *See* Specification at page 115, lines 19-28. Since Aβ deposits are the defining characteristic of amyloidosis, and since bathocuproine solubilizes Aβ deposits and prevents their formation, it follows that bathocuproine would be effective in treating amyloidosis.

Accordingly, the present invention provides methods and compositions for treating amyloidosis. Independent claim 1 is directed to a method of treating amyloidosis in a subject comprising administering to the subject an effective amount of (a) bathocuproine or a hydrophobic derivative thereof; and (b) one or more pharmaceutically acceptable carriers or diluents; for a time and under conditions to bring about the treatment; and wherein the bathocuproine or hydrophobic derivative thereof reduces, inhibits or otherwise interferes with Aβ-mediated production of radical oxygen species. Claim 2 is directed to the method of claim 1, further comprising administering to the subject an effective amount of indomethacin, or a pharmaceutically acceptable salt thereof. Support for claims 1 and 2 can be found throughout the specification, for example, at page 12, lines 5-15.

Claim 37 is directed to a pharmaceutical composition for treatment of conditions caused by amyloidosis, amyloid beta peptide (Aβ)-mediated reactive oxygen species (ROS) formation, or both, comprising: (a) bathocuproine or a hydrophobic derivative thereof; (b) indomethacin or a hydrophobic derivative thereof; and (c) one or more pharmaceutically

acceptable carriers or diluents. Support for claim 37 can be found throughout the specification, for example at page 16, line 3 through page 17, line 14.

VI. Issue on Appeal (37 C.F.R. § 1.192(c)(6))

The issue on appeal is whether claims 1, 2 and 37 are unpatentable under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

VII. Grouping of Claims (37 C.F.R. § 1.192(c)(7))

For the purpose of this appeal, the claims on appeal (1, 2 and 37) stand or fall together.

VIII. Argument (37 C.F.R. § 1.192(c)(8))

A. Legal Standard for Enablement

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable any person skilled in the art to make and use the claimed invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). *See also United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The factors to be considered when determining whether the necessary experimentation is "undue" include: (a) the breadth of the claims, (b) the nature of the invention, (c) the state of the prior art, (d) the level of one of ordinary skill,

(e) the level of predictability in the art, (f) the amount of direction provided by the inventor, (g) the existence of working examples, and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. Moreover, as long as the specification discloses at least one method for making and using the claimed invention, then the enablement requirement of 35 U.S.C. § 112, first paragraph is satisfied. *See Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998).

An Applicant is not limited to the confines of the specification to provide the necessary information to enable an invention. *See In re Howarth*, 654 F.2d 103, 105-6, 210 USPQ 689, 692 (CCPA 1981). An Applicant need not supply information that is well known in the art. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997); *Howarth*, 654 F.2d at 105-6, 210 USPQ at 692; *see also In re Brebner*, 455 F.2d 1402, 173 USPQ 169 (CCPA 1972) (finding a disclosure enabling because the procedure for making the starting material, although not disclosed, would have been known to one of ordinary skill in the art as evidenced by a Canadian patent). "'That which is common and well known is as if it were written out in the patent and delineated in the drawings.'" *Howarth*, 654 F.2d at 106, 210 USPQ at 692 (quoting *Webster Loom Co. v. Higgins* et al., 105 U.S. (15 Otto.) 580, 586 (1881)). Moreover, one of ordinary skill in the art is deemed to know not only what is considered well known in the art but also where to search for any needed starting materials. *See Id*; *see also Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1334, 65 USPQ2d 1385, 1400 (Fed. Cir. 2003) ("The specification need not explicitly teach those in the art how to make and use the invention; the [enablement] requirement is satisfied if, given what they already know, the specification

teaches those in the art enough that they can make and use the invention without 'undue experimentation.'")

In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). As enunciated by the Federal Circuit:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (emphasis in original; quoting *Marzocchi*, 439 F.2d at 224, 169 USPQ at 370).

B. The Claimed Invention is Fully Enabled

The claims involved in this appeal are directed to methods and pharmaceutical compositions for treating amyloidosis. The methods comprise administering to a subject an effective amount of bathocuproine or a hydrophobic derivative thereof and one or more pharmaceutically acceptable carriers or diluents. The pharmaceutical compositions comprise

bathocuproine or a hydrophobic derivative thereof and indomethacin or a hydrophobic derivative thereof.

Persons of ordinary skill in the art would have been able to practice the claimed methods and make and use the claimed pharmaceutical compositions using routine techniques. At the time of the effective filing date of this application, methods for formulating compounds into pharmaceutical compositions and administering such compositions to subjects were well known to persons of ordinary skill in the art. In addition, the specification provides specific guidance regarding the formulation and administration of metal chelators. For example, guidance is provided in the specification with respect to the frequency with which chelators may be administered. *See* Specification at page 45, lines 10-14. Moreover, the specification provides administration guidelines for the treatment of mildly, moderately and severely affected patients suffering from amyloidosis. *See* Specification at page 45, lines 15-27. Details regarding various routes of administration are also set forth. *See* Specification at page 46, line 8 through page 49, line 12.

The specification provides experimental evidence indicating that bathocuproine would be effective in treating amyloidosis when administered to a subject. For example, it was demonstrated that bathocuproine promotes the solubilization of Aβ from human brain homogenates. *See* Specification at page 91, line 18, through page 94, line 25. The inventors also discovered the relationship that exists between dose of chelator used and the extent to which Aβ is resolubilized. *See* Specification at page 94, lines 7-25. With regard to bathocuproine in particular, it was discovered that there is a clear dose-dependent increase in Aβ extraction from human brain. *See* Specification at page 94, lines 22-25, and Figure 19E. The inventors also found that, as with human brain, homogenates of brain cortical

tissue prepared from an amyloid-bearing APP transgenic mouse in the presence of a chelator exhibit enhanced extraction of pelletable Aβ. *See* Specification at page 95, lines 16-18. In addition, Aβ-mediated H_2O_2 formation, which is believed to be directly related to the neurodegeneration associated with Aβ deposits, was shown to be inhibited by bathocuproine. *See* Specification at page 84, line 13, through page 85, line 6. The specification therefore provides substantial experimental evidence to indicate that bathocuproine would be effective at treating amyloidosis when administered to a subject.

In view of the knowledge available in the art regarding the formulation and administration of pharmaceutical compositions in general, and the teachings in the specification relating to the formulation and administration of pharmaceutical compositions comprising bathocuproine in particular, a person of ordinary skill in the art would have been able to make, use and/or practice the full scope of subject matter encompassed by the present claims without undue experimentation.

C. Errors in the Rejection

In order to establish a *prima facie* case of non-enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513. Here, the Examiner has not set forth any specific evidence or sound scientific reasoning to indicate that making, using and/or practicing the subject matter encompassed by the present claims would have required undue experimentation. Thus, a *prima facie* case of non-enablement has not been established.

The Examiner's arguments in support of the enablement rejection can be divided into two categories:

(1) arguments relating to the ability of a skilled artisan to formulate pharmaceutical compositions comprising bathocuproine, and to effectively administer such compositions to a subject; and

(2) arguments relating to whether bathocuproine, when administered to a subject, would treat amyloidosis.

The vast majority of the arguments that have been set forth by the Examiner fall into the second category. An analysis of the specific arguments set forth by the Examiner under each category, and an explanation as to why they are legally insufficient to establish a *prima facie* case of non-enablement, is presented below.

1. Examiner's Arguments Relating to the Ability of A Skilled Artisan to Effectively Formulate and Administer Compositions Comprising Bathocuproine to A Subject

With respect to the first category, the Examiner has asserted that determining the amount of bathocuproine to be administered, the duration of treatment, and the routes of administration would have required undue experimentation on the part of a person of ordinary skill in the art. According to the Examiner:

> The skilled artisan must resort to trial and error experimentation to determine the optimal quantity of bathocuproine/indomethacin to be administered, as well as the duration of treatment and route of administration. Such trial and error experimentation is considered undue. There is little guidance in the specification at pg 45-49 regarding specific dosages, duration of treatment, and type of administration for bathocuproine.

Office Action dated May 22, 2003, page 5, line 18, through page 6, line 1. These assertions do not establish or contribute to a finding of non-enablement.

First, the Examiner has not put forth any evidence to support the assertions that determining (a) the optimal quantity of bathocuproine to be administered, (b) the duration of treatment, and/or (c) the route of administration would have required "trial and error experimentation." At the time of the effective filing date of the application, such parameters were routinely determined and optimized in the preparation and administration of pharmaceutical compositions. Moreover, the need for experimentation by itself is not sufficient to support a finding of non-enablement as long as the amount of experimentation is not regarded as undue. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *see also Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The Examiner has not explained why making and using pharmaceutical compositions comprising bathocuproine would have involved a greater amount of experimentation with respect to the determination of quantity, duration and routes of administration than is required for other compounds -- including metal chelators -- that have been routinely developed and administered effectively as pharmaceutical compositions in the art. *See* discussion below. Simply asserting that the determination of certain parameters would have required undue experimentation, without presenting any evidence to support this assertion, is legally insufficient to establish a *prima facie* case of non-enablement.

Second, the specification provides specific guidance as to the amount and timing of administration of chelators such as bathocuproine. *See* Specification at page 45, lines 5-27.

The specification also describes possible modes of administration. *See* Specification at page 46, line 8, through page 49, line 12. Importantly, the specification describes the relationship between bathocuproine concentration and Aβ solubilization. *See* Specification at page 90, line 12, through page 97, line 14, and Figure 19E. Such information would have instructed a skilled artisan as to the amount and frequency of administration of bathocuproine in order to achieve optimum therapeutic results.

Third, in addition to the teachings in the specification, a skilled artisan would have been guided by the knowledge generally available in the art regarding the preparation and administration of pharmaceutical compositions. A specification need not supply information that is well known in the art in order to satisfy the enablement requirement. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997); *See also Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art.") Since general methods for formulating and administering pharmaceutical compositions were well known in the art, such information should be regarded as supplementing the teachings in the specification.

A person of ordinary skill in the art, based on the specification and the knowledge generally available in the art, would have been able to determine the amount, duration and route of administration of bathocuproine in the context of the present invention using only routine experimentation. The Examiner has not presented any evidence to indicate otherwise. Therefore, the Examiner's arguments relating to the determination of these parameters do not support a *prima facie* case of non-enablement.

2. Examiner's Arguments Relating to Whether Bathocuproine, When Administered to a Subject, Would Treat Amyloidosis

As mentioned above, the majority of the arguments put forth by the Examiner relate to the issue of whether bathocuproine would be effective in the treatment of amyloidosis, *i.e.*, arguments as to whether or not the invention works. There are four general arguments that have been asserted under this category. First, the Examiner has argued that the specification lacks working examples showing the treatment of amyloidosis with bathocuproine. *See* Office Action dated August 26, 2002, page 5, lines 6-8. Second, the Examiner asserted that a skilled artisan would not be able to predict the effects that bathocuproine might have in a subject. *See* Office Action dated August 26, 2002, page 5, lines 11-16. Third, the Examiner has argued that the results set forth in the specification, demonstrating that bathocuproine can promote the extraction of Aβ from brain homogenates, may not be indicative of the results obtained with this chelator when administered to a subject. *See* Office Action dated May 22, 2003, page 7, lines 11-12. Fourth, it was argued that the positive clinical results obtained with the chelator clioquinol might not reflect the results that would be achieved using bathocuproine. *See* Office Action dated May 22, 2003, page 9, lines 9-14. Each of these arguments is addressed in turn below.

Before addressing the arguments individually, however, Appellants note that these arguments, as a whole, represent an improper attempt to shift the initial burden regarding the enablement of the invention to Appellants. The initial burden in demonstrating that a claimed invention is not enabled lies with the Examiner. *See Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513. Here, however, the Examiner has rejected the claims, not because there is any specific evidence to indicate that the invention *does not* work, but because, in the

Examiner's view, Appellants have not proven that the invention *does* work. A rejection under 35 U.S.C. § 112, first paragraph, cannot legally be established on this basis.

Notwithstanding the fact that it is not Appellants' initial burden to prove that the invention *is* enabled, Appellants have nonetheless presented several lines of evidence which support the conclusion that the administration of bathocuproine to a subject would be effective in treating amyloidosis. (These lines of evidence are discussed elsewhere in this Brief.) The Examiner has rejected these arguments on the basis that they do not *necessarily prove* that administering bathocuproine to a subject would be effective in the treatment of amyloidosis. Arguing that Appellants have not definitively shown that the invention *is* enabled, however, cannot satisfy the Examiner's burden of demonstrating that the invention *is not* enabled.

(a) Working Example

The Examiner stated that "the specification of the instant application does not teach treating amyloidosis in a subject. The specification does not teach any methods or working examples that indicate administration of bathocuproine or [bathocuproine]/indomethacin[1] to a subject." *See* Office Action dated August 26, 2002, page 5, lines 5-8. The absence of a working example, however, is not sufficient to establish a *prima facie* case of non-enablement. *See Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would have been able to practice it

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[1]The Office Action uses the expression "bathocuproine or *indomethacin*/ indomethacin." It appears, however, that the intended expression is "bathocuproine or *bathocuproine*/indomethacin."

without undue experimentation. *See In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). As discussed above, a person of ordinary skill in the art would have been able to make, use and practice the subject matter encompassed by the claims using routine methods in the art. The specification, along with the information generally available to persons of ordinary skill in the art, would have provided ample guidance in the preparation and administration of pharmaceutical compositions comprising bathocuproine to treat amyloidosis. No specific evidence has been presented to indicate otherwise. Therefore, the absence of a working example in the specification does not support the rejection for lack of enablement.

(b) Predictability

The Examiner has also made certain comments regarding the predictability of the invention. According to the Examiner, "[o]ne skilled in the art would also not be able to predict the effects that bathocuproine or [bathocuproine]/indomethacin might have in a subject since relevant literature reports that the search continues for a treatment that causes the mobilization of amyloid deposits. Office Action dated August 26, 2002, page 5, lines 11-14. To support this assertion, the Examiner cited Gillmore *et al.*, *Brit. J. Haematol. 99*:245-259 (1997) (copy submitted herewith as Exhibit 1), and stated that "Gilmore et al. also indicates that few clinical trials have been performed and the approach to treatment remain[s] somewhat empirical." Office Action dated August 26, 2002, page 5, lines14-16.

There is no logical connection between the statements in Gillmore and the Examiner's position that the effects of bathocuproine would be unpredictable. For instance,

it is unclear why a person of ordinary skill in the art would not be able to predict the effects of bathocuproine simply because "the search continues for a treatment that causes the mobilization of amyloid deposits." Furthermore, there is no discussion whatsoever in Gillmore relating to the use of metal chelators in treating amyloidosis. Gillmore, therefore, provides no basis for assessing the predictability of the effects of a chelator on a subject. At most, Gillmore indicates that, at the time of this reference, research in the area of amyloid deposit mobilization was *ongoing*. The fact that others in the art had not been able to accomplish the results provided by the present invention cannot form the basis for a proper enablement rejection. *See Gould,* 822 F.2d at 1078, 3 USPQ2d at 1304. There is nothing in Gillmore to suggest that the effects of bathocuproine or bathocuproine/indomethacin in a subject would have been regarded as unpredictable.

In addition to Gillmore, there are three references that have been cited by the Examiner to support the enablement rejection: Fonte *et al.*, *J. Alzheimer's Disease 3*:209-219 (2001), Cuajungco *et al.*, *Annals NY Acad. Sci. 290*:292-304 (2000), and Gnjec *et al.*, *Frontiers Biosci. 7*:1016-1023 (2002). (Copies of these references are submitted herewith as Exhibits 2, 3 and 4, respectively.) These references were originally cited to support the assertion that "the *in vitro* results obtained with bathocuproine may not necessarily be indicative of the results obtained with this metal chelator *in vivo*." Office Action dated May 22, 2003, page 7, line 11, through page 8, line 11. (The issue of whether the *in vitro* results are indicative of *in vivo* results is discussed specifically below.) In the Advisory Action it is stated that "the Examiner cited Fonte et al., Cuajungco et al., Gnjec et al., and Gillmore in the previous Office Action to indicate the unpredictability of the state of the art at the time the invention was made." Advisory Action dated November 12, 2003, page 2, lines 18-19.

These references, however, do not indicate that the administration of bathocuproine to a subject would have been regarded as unpredictable.

Fonte was cited to support the assertion that the chelator TPEN "is of limited benefit to patients because it is highly toxic." Office Action dated May 22, 2003, page 7, line 15 (citing Fonte at page 217, first paragraph). The statement in Fonte does not support the position that the administration of bathocuproine, or metal chelators in general, would have been unpredictable. Fonte simply indicates that TPEN might be of "*limited* benefit" due to its toxicity. The assertion that the benefits of TPEN may be "limited" does not suggest that TPEN would be ineffective in solubilizing Aβ in the brains of AD patients; "limited benefit" necessarily means at least *some* benefit. Moreover, the document cited in Fonte to support the statement that TPEN is "highly toxic," Adler *et al.*, *Toxicon. 35*:1089-1100 (1997), relates to the administration of TPEN to mice and states that "low doses of TPEN . . . were well tolerated." (*See* Adler, abstract, copy submitted herewith as exhibit 5.) Thus, it is likely that reducing the dose of TPEN would avoid any toxicity issues while nonetheless promoting Aβ resolubilization *in vivo*. Fonte does not support the position that administering metal chelators would have been unpredictable.

The Examiner cited Cuajungco for the propositions that: (a) "[the chelator] DFO [desferrioxamine] is a charged molecule that does not easily penetrate the blood-brain barrier and is easily degraded after administration," and (b) "the administration of DFO is associated with discouraging difficulties including the nonspecific problems of systemic metal ion depletion and the problem of administration of a twice-daily, painful intramuscular injection." Office Action dated May 22, 2003, page 7, lines 16-22.

Cuajungco does not indicate that the administration of metal chelators to subjects is unpredictable. Rather, Cuajungco supports the conclusion that administration of chelators would *not* have involved undue experimentation. Even though DFO supposedly causes "systemic metal ion depletion" and is administered by "painful intramuscular injection," it is clear that DFO is nonetheless effective at arresting the progression of Alzheimer's disease. Persons of ordinary skill in the art clearly were able to formulate and administer DFO in an effective manner notwithstanding the technical difficulties associated with this chelator. Thus, surmounting the potential technical difficulties associated with chelators (such as systemic ion depletion and convenient route of administration) cannot be regarded as undue experimentation. Cuajungco does not support the position that administering metal chelators would have been unpredictable.

Finally, Gnjec provides a general discussion of some of the technical considerations that are associated with chelator therapy. There is no evidence, however, to suggest that such considerations would amount to undue experimentation. The fact that chelators such as DFO and clioquinol (*see* discussion below) have been formulated into pharmaceutical compositions and have been successfully administered to subjects, thereby causing cognitive improvements in patients with Alzheimer's disease, indicates that addressing the technical considerations set forth in Gnjec can be accomplished using routine methods in the art and would not be regarded as undue experimentation. Gnjec therefore does not support the position that administering metal chelators would have been unpredictable.

The Examiner has not presented any specific evidence to indicate that the administration of bathocuproine to a subject would have been regarded as unpredictable. The references cited by the Examiner do not support the enablement rejection. Gillmore

does not relate to chelators at all, Fonte simply indicates that the benefits of TPEN may be limited due to its toxicity at high doses, Cuajungco demonstrates that DFO can be effectively administered to treat Alzheimer's disease despite certain technical issues relating to this chelator, and Gnjec merely outlines certain technical considerations related to the administration of chelators generally. Metal chelators have been formulated into pharmaceutical compositions and have been successfully administered to subjects for therapeutic purposes. Thus, it is clear that the administration of chelators was not regarded as unpredictable.

(c) In Vitro Results

The Examples in the specification support the conclusion that bathocuproine would be effective at treating amyloidosis when administered to a subject. As discussed above, the specification demonstrates that bathocuproine promotes the solubilization of Aβ from human brain homogenates. The existing evidence and teachings in the art strongly support the correlation between the *in vitro* results presented in the specification and the results that would be obtained a subject.

First, the physiological conditions that exist in brain homogenates (*e.g.*, pH, ion concentration, macromolecular content, etc.) closely approximate the conditions found in the brain tissue environment *in vivo*.

Second, it was known in the art at the time the application was filed that the regulation of zinc and copper in the brain is abnormal in AD and that these metals are integral components of the Aβ deposits in the brains of AD patients. *See* Specification at page 90, line 27 through page 91, line 4. It was also observed that zinc- and copper-specific

chelators dramatically redissolve a significant proportion of Aβ extracted from post-mortem AD affected brain tissue. *See* Specification at page 91, lines 4-8.

Third, as mentioned above, a particular strategy described in the art that resulted in slowing the progression of AD involved the intramuscular administration of DFO to Alzheimer's disease patients. *See* Crapper-McLachlan *et al.*, *Lancet 337*:1304-1308 (1991) (cited in the Specification at page 91, lines 9-16).

Fourth, there is at least one additional example in the art of a chelator (clioquinol) that was first shown to be effective in solubilizing Aβ deposits *in vitro,* and was subsequently found to be effective in the treatment of Alzheimer's disease when administered to patients. (The parallels between the present invention and the results that were obtained with clioquinol are discussed in more detail below.)

In view of the foregoing, a person of ordinary skill in the art would have concluded that the *in vitro* results obtained with bathocuproine (and the other chelators described in the specification) are indicative of the results that would be achieved when the chelator is administered to a subject; *i.e.*, it is reasonable to conclude that the administration of bathocuproine to a subject would result in the treatment of amyloidosis. There has been no specific evidence presented to contradict the logic underlying this conclusion.

The Examiner has not presented any specific evidence to suggest that, even though bathocuproine solubilizes Aβ *in vitro*, this chelator would be ineffective in treating amyloidosis in a subject. The Examiner originally cited Fonte, Cuajungco and Gnjec as supporting the position that *in vitro* results with a metal chelator may not be indicative of *in vivo* results. *See* Office Action dated May 22, 2003, page 7, line 11, through page 8, line 11. (Appellants note that in the Advisory Action the Examiner stated that these references

were simply intended to indicate "the unpredictability of the state of the art." *See* Advisory Action at page 2, line 19). Regardless of which argument these references were cited to support, none of the references address the issue of whether *in vitro* results with a metal chelator are indicative of *in vivo* results. Therefore, no evidence has been presented to support the assertion that the *in vitro* results with bathocuproine are not indicative of the biological results that would be obtained when bathocuproine is administered to a subject.

The Examiner stated that "the *in vitro* results obtained with bathocuproine *may not necessarily be indicative* of the results obtained with this metal chelator *in vivo*." Office Action dated May 22, 2003, page 7, lines 11-12 (emphasis added). In other words, the Examiner has indicated that the enablement rejection would be maintained unless it is shown that the *in vitro* results with bathocuproine are "*necessarily . . . indicative*" of the results that would be obtained with bathocuproine *in vivo*. As mentioned previously, the Examiner has the initial burden of showing that the invention is *not* enabled. *See Marzocchi*, 439 F.2d at 224, 169 USPQ at 370 ("it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.") It is therefore legally improper for the Examiner to require proof that bathocuproine would *necessarily* treat amyloidosis in a subject when no specific evidence to the contrary has been presented.

Even though it is not Appellants' initial burden to establish that the invention is enabled, Appellants have nonetheless presented several lines of evidence to indicate that the *in vitro* results with bathocuproine reflect the results that would be obtained when this chelator is administered to a subject. *See* discussion set forth above. The Examiner has not

presented any evidence to suggest that this is not the case. Thus, a *prima facie* case of non-enablement has not been established.

(d) Clioquinol

As mentioned above, the metal chelator clioquinol has been shown to be effective in the treatment of Alzheimer's disease. *See* Ritchie *et al.*, "Metal complexation with iodochlorhydroxyquin (clioquinol) targeting Aβ amyloid deposition and toxicity in Alzheimer's disease: proof-of-concept and safety" (unpublished manuscript, submitted for publication) (2003) (copy attached hereto as Exhibit 6). Clioquinol, like bathocuproine, was first shown to promote the solubilization of Aβ *in vitro*. *See* Cherny *et al.*, *Neuron 30*:665-676 (2001) (copy attached hereto as Exhibit 7). The *in vitro* results with clioquinol provided the foundation for subsequent clinical work with this chelator.

The results with clioquinol support Appellants' position that the present invention is enabled in two respects. First, the clioquinol example shows that a chelator's ability to promote Aβ solubilization *in vitro* likely reflects its ability to treat conditions associated with Aβ deposition *in vivo*. Second, the results with clioquinol show that persons of ordinary skill in the art were able to successfully formulate and administer a metal chelator to subjects without undue experimentation. Since persons of ordinary skill in the art were able to successfully formulate and administer clioquinol using only routine methods, there is no reason to believe that persons of ordinary skill in the art could not have also been able to successfully formulate and administer bathocuproine. The Examiner has not provided any evidence or scientifically sound reasoning to indicate that there is a difference in the burden

on a person of ordinary skill in the art to formulate bathocuproine for administration to a subject as compared to the burden required to formulate and administer clioquinol.

The Examiner has not presented any evidence or scientifically sound reasoning to indicate that the success obtained with clioquinol would not have also been achieved with bathocuproine. The Examiner simply stated that clioquinol is specific for copper and zinc ions and has a different chemical make-up and structure than bathocuproine, which is specific for copper. *See* Office Action dated May 22, 2003, page 9, lines 12-16. The Examiner has not explained why such differences at the chemical level make it unlikely that bathocuproine would exert therapeutic effects when administered to a subject. Regardless of whether clioquinol differs from bathocuproine at the chemical level, the fact remains that persons of ordinary skill in the art were clearly able to formulate and administer metal chelators to subjects for therapeutic purposes without undue experimentation.

Finally, the Examiner's arguments relating to whether the results with clioquinol suggest similar results with bathocuproine (as well as the arguments relating to whether the *in vitro* results with bathocuproine are indicative of *in vivo* results with this chelator) are tangential to the basic inquiry in a proper enablement analysis. That is, the Examiner's arguments are aimed at rebutting Appellants' assertions that the invention *is* enabled. The Examiner, however, has not demonstrated that making and using the claimed invention would have required undue experimentation. The Examiner's position is that Appellants have not proven that the results with clioquinol reflect similar results that would be obtained with bathocuproine. According to the Examiner, "[b]athocuproine *may* have different physiological effects after administration to a subject than does clioquinol." Office Action dated May 22, 2003, page 9, lines 15-16, emphasis added. Such arguments, however, do not

satisfy the Examiner's initial burden of showing that the claimed invention is *not* enabled. Since it is not Appellants' initial burden to prove that the invention *is* enabled, a *prima facie* case of non-enablement cannot be established by arguing that Appellant's have not definitively proven enablement. Therefore, the Examiner's arguments as to whether the results with clioquinol reflect the results that would be obtained with bathocuproine cannot support a *prima facie* case of non-enablement.

D. Summary

A person of ordinary skill in the art would have been able to make and use the subject matter encompassed by the present claims without undue experimentation. The specification provides specific guidance regarding the formulation and administration of bathocuproine (and bathocuproine/indomethacin) in order to treat amyloidosis in a subject. In addition to the teachings in the specification, a skilled artisan would have been guided by the knowledge in the art relating to the formulation and administration of pharmaceutical compositions for therapeutic purposes. The examples in the specification along with other evidence in the art (*e.g.*, the results obtained with clioquinol) strongly indicate that bathocuproine would be successful in treating amyloidosis in a subject.

No specific evidence has been presented to suggest that the claimed invention is not enabled. The arguments that have been presented do not address the primary issue of whether or not a skilled person in the art would have been able to make and/or use the subject matter of the present claims without undue experimentation. In essence, the Examiner's argument is that Appellants have failed to definitively prove that the invention would function as intended, *i.e.*, that bathocuproine would -- without question -- treat

amyloidosis when administered to a subject. Appellants believe that substantial evidence has been presented to indicate that the invention would function as intended. Moreover, under 35 U.S.C. § 112, first paragraph, argumentation as to whether an Applicant has proven that the invention *is enabled* cannot substitute for the Examiner's primary responsibility of presenting particular evidence that the invention is *not enabled.* Thus, the Examiner's arguments are legally insufficient to establish a *prima facie* case of non-enablement.

In view of the foregoing remarks, Appellants respectfully request that the Board reverse the Examiner's § 112, first paragraph rejection of claims 1, 2 and 37 and remand this application for issue.

Respectfully submitted,

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IX. Appendix (37 C.F.R. § 1.192(c)(9))

1. A method of treating amyloidosis in a subject, said method comprising administering to said subject an effective amount of (a) bathocuproine or a hydrophobic derivative thereof; and (b) one or more pharmaceutically acceptable carriers or diluents; for a time and under conditions to bring about said treatment; and

wherein said bathocuproine or hydrophobic derivative thereof reduces, inhibits or otherwise interferes with amyloid beta peptide (Aβ)-mediated production of radical oxygen species.

2. The method of claim 1 further comprising administering to the subject an effective amount of indomethacin, or a pharmaceutically acceptable salt thereof.

37. A pharmaceutical composition for treatment of conditions caused by amyloidosis, amyloid beta peptide (Aβ)-mediated reactive oxygen species (ROS) formation, or both, comprising: (a) bathocuproine or a hydrophobic derivative thereof; (b) indomethacin or a hydrophobic derivative thereof; and (c) one or more pharmaceutically acceptable carriers or diluents.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2953
BUSH *et al.*	Art Unit: 1647
Appl. No. 09/380,704	Examiner: Bunner, B.
§ 371 Date: June 6, 2000	Atty. Docket: 0609.4350001/JAG/FRC
For: **A Composition Comprising a Metal Chelator and a Method of Treating Amyloidosis by Administering the Metal Chelator**	

Brief on Appeal Under 37 C.F.R. § 1.192

Mail Stop Appeal Brief - Patents

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

A Notice of Appeal from the final rejection of claims 1, 2 and 37 was filed on October 17, 2003. Appellants hereby file this Appeal Brief in triplicate, together with the required brief filing fee.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

I. Real Parties in Interest (37 C.F.R. § 1.192(c)(1))

The real parties in interest in this appeal are The General Hospital Corporation and Prana Biotechnology Limited.

II. Related Appeals and Interferences (37 C.F.R. § 1.192(c)(2))

Appellants' undersigned representative is not aware of any appeals or interferences related to the captioned application.

III. Status of Claims (37 C.F.R. § 1.192(c)(3))

The captioned application was filed under 35 U.S.C. § 371 on September 8, 1999 and is a U.S. national phase application of international application No. PCT/US98/04683, filed on March 11, 1998. As originally filed, the application contained a total of 94 claims.

In a Preliminary Amendment filed on May 17, 2002, claims 3-36, 39-52 and 54-94 were cancelled, and claims 1 and 37 were amended.

In an Amendment filed on February 26, 2003, claims 1, 2, 37, 38 and 53 were amended.

In an Amendment filed on October 17, 2003, claim 38 was cancelled and claims 1 and 37 were amended.

Claims 1, 2, 37 and 53 are pending in the application.

Claim 53 is allowed.

Claims 1, 2 and 37 are now on appeal. A copy of the claims on appeal can be found in the attached Appendix.

IV. Status of Amendments (37 C.F.R. § 1.192(c)(4))

All amendments have been entered. No amendments have been filed subsequent to the issuance of the final Office Action dated May 22, 2003.

V. Summary of Invention (37 C.F.R. § 1.192(c)(5))

Amyloidosis is a general term which refers to any disease characterized by the extracellular accumulation of amyloid beta (Aβ) in organs and tissues. *See* Specification at page 24, lines 15-16. For example, Aβ deposits in the brain are believed to be responsible for the neuronal defects that lead to Alzheimer's disease. Aβ deposits are concentrated in regions of neuronal cell death in the brains of Alzheimer's disease patients. *See* Specification at page 1, lines 16-25. In addition, polymers of Aβ are neurotoxic to neurons in culture. *See* Specification at page 2, lines 11-25. Aβ-mediated neurotoxicity may be the result of the production of reactive oxygen species (ROS) such as hydroxyl radical (OH•), superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2). *See* Specification at page 41, line 13 through page 42, line 4. Since Aβ deposits are believed to be the cause of the tissue toxicity that is associated with amyloidosis, agents that interfere with and/or reverse Aβ deposition are sought after to treat amyloidosis.

The regulation of zinc and copper is abnormal in the brains of Alzheimer's disease patients. It has been found that zinc and copper are integral components of Aβ deposits. *See* Specification at page 90, line 23, through page 91, line 4. Experiments have shown that Aβ deposition is mediated by the presence of Zn^{2+} and Cu^{2+} ions. *See* Specification at page 3, lines 5-10. For example, Zn^{2+} and Cu^{2+} dramatically induce the precipitation of Aβ *in vitro*. *See* Specification at page 53, line 24, through page 54, line 14. The present inventors have

shown that metal chelators (*i.e.*, agents that reduce the amount of free metal ions) inhibit Aβ deposit formation and solubilize Aβ aggregates. *See, e.g.*, Specification at page 90, line 12 through page 97, line 14 (Example 5). Bathocuproine is an exemplary metal chelator. Bathocuproine was found by the inventors to solubilize Aβ deposits and interfere significantly with copper-mediated generation of Aβ polymers. *See* Specification at page 115, lines 19-28. Since Aβ deposits are the defining characteristic of amyloidosis, and since bathocuproine solubilizes Aβ deposits and prevents their formation, it follows that bathocuproine would be effective in treating amyloidosis.

Accordingly, the present invention provides methods and compositions for treating amyloidosis. Independent claim 1 is directed to a method of treating amyloidosis in a subject comprising administering to the subject an effective amount of (a) bathocuproine or a hydrophobic derivative thereof; and (b) one or more pharmaceutically acceptable carriers or diluents; for a time and under conditions to bring about the treatment; and wherein the bathocuproine or hydrophobic derivative thereof reduces, inhibits or otherwise interferes with Aβ-mediated production of radical oxygen species. Claim 2 is directed to the method of claim 1, further comprising administering to the subject an effective amount of indomethacin, or a pharmaceutically acceptable salt thereof. Support for claims 1 and 2 can be found throughout the specification, for example, at page 12, lines 5-15.

Claim 37 is directed to a pharmaceutical composition for treatment of conditions caused by amyloidosis, amyloid beta peptide (Aβ)-mediated reactive oxygen species (ROS) formation, or both, comprising: (a) bathocuproine or a hydrophobic derivative thereof; (b) indomethacin or a hydrophobic derivative thereof; and (c) one or more pharmaceutically

acceptable carriers or diluents. Support for claim 37 can be found throughout the specification, for example at page 16, line 3 through page 17, line 14.

VI. Issue on Appeal (37 C.F.R. § 1.192(c)(6))

The issue on appeal is whether claims 1, 2 and 37 are unpatentable under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

VII. Grouping of Claims (37 C.F.R. § 1.192(c)(7))

For the purpose of this appeal, the claims on appeal (1, 2 and 37) stand or fall together.

VIII. Argument (37 C.F.R. § 1.192(c)(8))

A. Legal Standard for Enablement

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable any person skilled in the art to make and use the claimed invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). *See also United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The factors to be considered when determining whether the necessary experimentation is "undue" include: (a) the breadth of the claims, (b) the nature of the invention, (c) the state of the prior art, (d) the level of one of ordinary skill,

(e) the level of predictability in the art, (f) the amount of direction provided by the inventor, (g) the existence of working examples, and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. Moreover, as long as the specification discloses at least one method for making and using the claimed invention, then the enablement requirement of 35 U.S.C. § 112, first paragraph is satisfied. *See Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998).

An Applicant is not limited to the confines of the specification to provide the necessary information to enable an invention. *See In re Howarth*, 654 F.2d 103, 105-6, 210 USPQ 689, 692 (CCPA 1981). An Applicant need not supply information that is well known in the art. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997); *Howarth*, 654 F.2d at 105-6, 210 USPQ at 692; *see also In re Brebner*, 455 F.2d 1402, 173 USPQ 169 (CCPA 1972) (finding a disclosure enabling because the procedure for making the starting material, although not disclosed, would have been known to one of ordinary skill in the art as evidenced by a Canadian patent). "'That which is common and well known is as if it were written out in the patent and delineated in the drawings.'" *Howarth*, 654 F.2d at 106, 210 USPQ at 692 (quoting *Webster Loom Co. v. Higgins* et al., 105 U.S. (15 Otto.) 580, 586 (1881)). Moreover, one of ordinary skill in the art is deemed to know not only what is considered well known in the art but also where to search for any needed starting materials. *See Id*; *see also Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1334, 65 USPQ2d 1385, 1400 (Fed. Cir. 2003) ("The specification need not explicitly teach those in the art how to make and use the invention; the [enablement] requirement is satisfied if, given what they already know, the specification

teaches those in the art enough that they can make and use the invention without 'undue experimentation.'")

In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). As enunciated by the Federal Circuit:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (emphasis in original; quoting *Marzocchi*, 439 F.2d at 224, 169 USPQ at 370).

B. The Claimed Invention is Fully Enabled

The claims involved in this appeal are directed to methods and pharmaceutical compositions for treating amyloidosis. The methods comprise administering to a subject an effective amount of bathocuproine or a hydrophobic derivative thereof and one or more pharmaceutically acceptable carriers or diluents. The pharmaceutical compositions comprise

bathocuproine or a hydrophobic derivative thereof and indomethacin or a hydrophobic derivative thereof.

Persons of ordinary skill in the art would have been able to practice the claimed methods and make and use the claimed pharmaceutical compositions using routine techniques. At the time of the effective filing date of this application, methods for formulating compounds into pharmaceutical compositions and administering such compositions to subjects were well known to persons of ordinary skill in the art. In addition, the specification provides specific guidance regarding the formulation and administration of metal chelators. For example, guidance is provided in the specification with respect to the frequency with which chelators may be administered. *See* Specification at page 45, lines 10-14. Moreover, the specification provides administration guidelines for the treatment of mildly, moderately and severely affected patients suffering from amyloidosis. *See* Specification at page 45, lines 15-27. Details regarding various routes of administration are also set forth. *See* Specification at page 46, line 8 through page 49, line 12.

The specification provides experimental evidence indicating that bathocuproine would be effective in treating amyloidosis when administered to a subject. For example, it was demonstrated that bathocuproine promotes the solubilization of Aβ from human brain homogenates. *See* Specification at page 91, line 18, through page 94, line 25. The inventors also discovered the relationship that exists between dose of chelator used and the extent to which Aβ is resolubilized. *See* Specification at page 94, lines 7-25. With regard to bathocuproine in particular, it was discovered that there is a clear dose-dependent increase in Aβ extraction from human brain. *See* Specification at page 94, lines 22-25, and Figure 19E. The inventors also found that, as with human brain, homogenates of brain cortical

tissue prepared from an amyloid-bearing APP transgenic mouse in the presence of a chelator exhibit enhanced extraction of pelletable Aβ. *See* Specification at page 95, lines 16-18. In addition, Aβ-mediated H_2O_2 formation, which is believed to be directly related to the neurodegeneration associated with Aβ deposits, was shown to be inhibited by bathocuproine. *See* Specification at page 84, line 13, through page 85, line 6. The specification therefore provides substantial experimental evidence to indicate that bathocuproine would be effective at treating amyloidosis when administered to a subject.

In view of the knowledge available in the art regarding the formulation and administration of pharmaceutical compositions in general, and the teachings in the specification relating to the formulation and administration of pharmaceutical compositions comprising bathocuproine in particular, a person of ordinary skill in the art would have been able to make, use and/or practice the full scope of subject matter encompassed by the present claims without undue experimentation.

C. Errors in the Rejection

In order to establish a *prima facie* case of non-enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513. Here, the Examiner has not set forth any specific evidence or sound scientific reasoning to indicate that making, using and/or practicing the subject matter encompassed by the present claims would have required undue experimentation. Thus, a *prima facie* case of non-enablement has not been established.

The Examiner's arguments in support of the enablement rejection can be divided into two categories:

(1) arguments relating to the ability of a skilled artisan to formulate pharmaceutical compositions comprising bathocuproine, and to effectively administer such compositions to a subject; and

(2) arguments relating to whether bathocuproine, when administered to a subject, would treat amyloidosis.

The vast majority of the arguments that have been set forth by the Examiner fall into the second category. An analysis of the specific arguments set forth by the Examiner under each category, and an explanation as to why they are legally insufficient to establish a *prima facie* case of non-enablement, is presented below.

1. Examiner's Arguments Relating to the Ability of A Skilled Artisan to Effectively Formulate and Administer Compositions Comprising Bathocuproine to A Subject

With respect to the first category, the Examiner has asserted that determining the amount of bathocuproine to be administered, the duration of treatment, and the routes of administration would have required undue experimentation on the part of a person of ordinary skill in the art. According to the Examiner:

> The skilled artisan must resort to trial and error experimentation to determine the optimal quantity of bathocuproine/indomethacin to be administered, as well as the duration of treatment and route of administration. Such trial and error experimentation is considered undue. There is little guidance in the specification at pg 45-49 regarding specific dosages, duration of treatment, and type of administration for bathocuproine.

Office Action dated May 22, 2003, page 5, line 18, through page 6, line 1. These assertions do not establish or contribute to a finding of non-enablement.

First, the Examiner has not put forth any evidence to support the assertions that determining (a) the optimal quantity of bathocuproine to be administered, (b) the duration of treatment, and/or (c) the route of administration would have required "trial and error experimentation." At the time of the effective filing date of the application, such parameters were routinely determined and optimized in the preparation and administration of pharmaceutical compositions. Moreover, the need for experimentation by itself is not sufficient to support a finding of non-enablement as long as the amount of experimentation is not regarded as undue. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *see also Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The Examiner has not explained why making and using pharmaceutical compositions comprising bathocuproine would have involved a greater amount of experimentation with respect to the determination of quantity, duration and routes of administration than is required for other compounds -- including metal chelators -- that have been routinely developed and administered effectively as pharmaceutical compositions in the art. *See* discussion below. Simply asserting that the determination of certain parameters would have required undue experimentation, without presenting any evidence to support this assertion, is legally insufficient to establish a *prima facie* case of non-enablement.

Second, the specification provides specific guidance as to the amount and timing of administration of chelators such as bathocuproine. *See* Specification at page 45, lines 5-27.

The specification also describes possible modes of administration. *See* Specification at page 46, line 8, through page 49, line 12. Importantly, the specification describes the relationship between bathocuproine concentration and Aβ solubilization. *See* Specification at page 90, line 12, through page 97, line 14, and Figure 19E. Such information would have instructed a skilled artisan as to the amount and frequency of administration of bathocuproine in order to achieve optimum therapeutic results.

Third, in addition to the teachings in the specification, a skilled artisan would have been guided by the knowledge generally available in the art regarding the preparation and administration of pharmaceutical compositions. A specification need not supply information that is well known in the art in order to satisfy the enablement requirement. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997); *See also Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art.") Since general methods for formulating and administering pharmaceutical compositions were well known in the art, such information should be regarded as supplementing the teachings in the specification.

A person of ordinary skill in the art, based on the specification and the knowledge generally available in the art, would have been able to determine the amount, duration and route of administration of bathocuproine in the context of the present invention using only routine experimentation. The Examiner has not presented any evidence to indicate otherwise. Therefore, the Examiner's arguments relating to the determination of these parameters do not support a *prima facie* case of non-enablement.

2. Examiner's Arguments Relating to Whether Bathocuproine, When Administered to a Subject, Would Treat Amyloidosis

As mentioned above, the majority of the arguments put forth by the Examiner relate to the issue of whether bathocuproine would be effective in the treatment of amyloidosis, *i.e.*, arguments as to whether or not the invention works. There are four general arguments that have been asserted under this category. First, the Examiner has argued that the specification lacks working examples showing the treatment of amyloidosis with bathocuproine. *See* Office Action dated August 26, 2002, page 5, lines 6-8. Second, the Examiner asserted that a skilled artisan would not be able to predict the effects that bathocuproine might have in a subject. *See* Office Action dated August 26, 2002, page 5, lines 11-16. Third, the Examiner has argued that the results set forth in the specification, demonstrating that bathocuproine can promote the extraction of Aβ from brain homogenates, may not be indicative of the results obtained with this chelator when administered to a subject. *See* Office Action dated May 22, 2003, page 7, lines 11-12. Fourth, it was argued that the positive clinical results obtained with the chelator clioquinol might not reflect the results that would be achieved using bathocuproine. *See* Office Action dated May 22, 2003, page 9, lines 9-14. Each of these arguments is addressed in turn below.

Before addressing the arguments individually, however, Appellants note that these arguments, as a whole, represent an improper attempt to shift the initial burden regarding the enablement of the invention to Appellants. The initial burden in demonstrating that a claimed invention is not enabled lies with the Examiner. *See Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513. Here, however, the Examiner has rejected the claims, not because there is any specific evidence to indicate that the invention *does not* work, but because, in the

Examiner's view, Appellants have not proven that the invention *does* work. A rejection under 35 U.S.C. § 112, first paragraph, cannot legally be established on this basis.

Notwithstanding the fact that it is not Appellants' initial burden to prove that the invention *is* enabled, Appellants have nonetheless presented several lines of evidence which support the conclusion that the administration of bathocuproine to a subject would be effective in treating amyloidosis. (These lines of evidence are discussed elsewhere in this Brief.) The Examiner has rejected these arguments on the basis that they do not *necessarily prove* that administering bathocuproine to a subject would be effective in the treatment of amyloidosis. Arguing that Appellants have not definitively shown that the invention *is* enabled, however, cannot satisfy the Examiner's burden of demonstrating that the invention *is not* enabled.

(a) Working Example

The Examiner stated that "the specification of the instant application does not teach treating amyloidosis in a subject. The specification does not teach any methods or working examples that indicate administration of bathocuproine or [bathocuproine]/indomethacin[1] to a subject." *See* Office Action dated August 26, 2002, page 5, lines 5-8. The absence of a working example, however, is not sufficient to establish a *prima facie* case of non-enablement. *See Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would have been able to practice it

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[1]The Office Action uses the expression "bathocuproine or *indomethacin*/indomethacin." It appears, however, that the intended expression is "bathocuproine or *bathocuproine*/indomethacin."

without undue experimentation. *See In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). As discussed above, a person of ordinary skill in the art would have been able to make, use and practice the subject matter encompassed by the claims using routine methods in the art. The specification, along with the information generally available to persons of ordinary skill in the art, would have provided ample guidance in the preparation and administration of pharmaceutical compositions comprising bathocuproine to treat amyloidosis. No specific evidence has been presented to indicate otherwise. Therefore, the absence of a working example in the specification does not support the rejection for lack of enablement.

(b) Predictability

The Examiner has also made certain comments regarding the predictability of the invention. According to the Examiner, "[o]ne skilled in the art would also not be able to predict the effects that bathocuproine or [bathocuproine]/indomethacin might have in a subject since relevant literature reports that the search continues for a treatment that causes the mobilization of amyloid deposits. Office Action dated August 26, 2002, page 5, lines 11-14. To support this assertion, the Examiner cited Gillmore *et al.*, *Brit. J. Haematol. 99*:245-259 (1997) (copy submitted herewith as Exhibit 1), and stated that "Gilmore et al. also indicates that few clinical trials have been performed and the approach to treatment remain[s] somewhat empirical." Office Action dated August 26, 2002, page 5, lines14-16.

There is no logical connection between the statements in Gillmore and the Examiner's position that the effects of bathocuproine would be unpredictable. For instance,

it is unclear why a person of ordinary skill in the art would not be able to predict the effects of bathocuproine simply because "the search continues for a treatment that causes the mobilization of amyloid deposits." Furthermore, there is no discussion whatsoever in Gillmore relating to the use of metal chelators in treating amyloidosis. Gillmore, therefore, provides no basis for assessing the predictability of the effects of a chelator on a subject. At most, Gillmore indicates that, at the time of this reference, research in the area of amyloid deposit mobilization was *ongoing*. The fact that others in the art had not been able to accomplish the results provided by the present invention cannot form the basis for a proper enablement rejection. *See Gould,* 822 F.2d at 1078, 3 USPQ2d at 1304. There is nothing in Gillmore to suggest that the effects of bathocuproine or bathocuproine/indomethacin in a subject would have been regarded as unpredictable.

In addition to Gillmore, there are three references that have been cited by the Examiner to support the enablement rejection: Fonte *et al.*, *J. Alzheimer's Disease 3*:209-219 (2001), Cuajungco *et al.*, *Annals NY Acad. Sci. 290*:292-304 (2000), and Gnjec *et al.*, *Frontiers Biosci. 7*:1016-1023 (2002). (Copies of these references are submitted herewith as Exhibits 2, 3 and 4, respectively.) These references were originally cited to support the assertion that "the *in vitro* results obtained with bathocuproine may not necessarily be indicative of the results obtained with this metal chelator *in vivo*." Office Action dated May 22, 2003, page 7, line 11, through page 8, line 11. (The issue of whether the *in vitro* results are indicative of *in vivo* results is discussed specifically below.) In the Advisory Action it is stated that "the Examiner cited Fonte et al., Cuajungco et al., Gnjec et al., and Gillmore in the previous Office Action to indicate the unpredictability of the state of the art at the time the invention was made." Advisory Action dated November 12, 2003, page 2, lines 18-19.

These references, however, do not indicate that the administration of bathocuproine to a subject would have been regarded as unpredictable.

Fonte was cited to support the assertion that the chelator TPEN "is of limited benefit to patients because it is highly toxic." Office Action dated May 22, 2003, page 7, line 15 (citing Fonte at page 217, first paragraph). The statement in Fonte does not support the position that the administration of bathocuproine, or metal chelators in general, would have been unpredictable. Fonte simply indicates that TPEN might be of "*limited* benefit" due to its toxicity. The assertion that the benefits of TPEN may be "limited" does not suggest that TPEN would be ineffective in solubilizing Aβ in the brains of AD patients; "limited benefit" necessarily means at least *some* benefit. Moreover, the document cited in Fonte to support the statement that TPEN is "highly toxic," Adler *et al.*, *Toxicon. 35*:1089-1100 (1997), relates to the administration of TPEN to mice and states that "low doses of TPEN . . . were well tolerated." (*See* Adler, abstract, copy submitted herewith as exhibit 5.) Thus, it is likely that reducing the dose of TPEN would avoid any toxicity issues while nonetheless promoting Aβ resolubilization *in vivo*. Fonte does not support the position that administering metal chelators would have been unpredictable.

The Examiner cited Cuajungco for the propositions that: (a) "[the chelator] DFO [desferrioxamine] is a charged molecule that does not easily penetrate the blood-brain barrier and is easily degraded after administration," and (b) "the administration of DFO is associated with discouraging difficulties including the nonspecific problems of systemic metal ion depletion and the problem of administration of a twice-daily, painful intramuscular injection." Office Action dated May 22, 2003, page 7, lines 16-22.

Cuajungco does not indicate that the administration of metal chelators to subjects is unpredictable. Rather, Cuajungco supports the conclusion that administration of chelators would *not* have involved undue experimentation. Even though DFO supposedly causes "systemic metal ion depletion" and is administered by "painful intramuscular injection," it is clear that DFO is nonetheless effective at arresting the progression of Alzheimer's disease. Persons of ordinary skill in the art clearly were able to formulate and administer DFO in an effective manner notwithstanding the technical difficulties associated with this chelator. Thus, surmounting the potential technical difficulties associated with chelators (such as systemic ion depletion and convenient route of administration) cannot be regarded as undue experimentation. Cuajungco does not support the position that administering metal chelators would have been unpredictable.

Finally, Gnjec provides a general discussion of some of the technical considerations that are associated with chelator therapy. There is no evidence, however, to suggest that such considerations would amount to undue experimentation. The fact that chelators such as DFO and clioquinol (*see* discussion below) have been formulated into pharmaceutical compositions and have been successfully administered to subjects, thereby causing cognitive improvements in patients with Alzheimer's disease, indicates that addressing the technical considerations set forth in Gnjec can be accomplished using routine methods in the art and would not be regarded as undue experimentation. Gnjec therefore does not support the position that administering metal chelators would have been unpredictable.

The Examiner has not presented any specific evidence to indicate that the administration of bathocuproine to a subject would have been regarded as unpredictable. The references cited by the Examiner do not support the enablement rejection. Gillmore

does not relate to chelators at all, Fonte simply indicates that the benefits of TPEN may be limited due to its toxicity at high doses, Cuajungco demonstrates that DFO can be effectively administered to treat Alzheimer's disease despite certain technical issues relating to this chelator, and Gnjec merely outlines certain technical considerations related to the administration of chelators generally. Metal chelators have been formulated into pharmaceutical compositions and have been successfully administered to subjects for therapeutic purposes. Thus, it is clear that the administration of chelators was not regarded as unpredictable.

(c) In Vitro Results

The Examples in the specification support the conclusion that bathocuproine would be effective at treating amyloidosis when administered to a subject. As discussed above, the specification demonstrates that bathocuproine promotes the solubilization of Aβ from human brain homogenates. The existing evidence and teachings in the art strongly support the correlation between the *in vitro* results presented in the specification and the results that would be obtained a subject.

First, the physiological conditions that exist in brain homogenates (*e.g.*, pH, ion concentration, macromolecular content, etc.) closely approximate the conditions found in the brain tissue environment *in vivo*.

Second, it was known in the art at the time the application was filed that the regulation of zinc and copper in the brain is abnormal in AD and that these metals are integral components of the Aβ deposits in the brains of AD patients. *See* Specification at page 90, line 27 through page 91, line 4. It was also observed that zinc- and copper-specific

chelators dramatically redissolve a significant proportion of Aβ extracted from post-mortem AD affected brain tissue. *See* Specification at page 91, lines 4-8.

Third, as mentioned above, a particular strategy described in the art that resulted in slowing the progression of AD involved the intramuscular administration of DFO to Alzheimer's disease patients. *See* Crapper-McLachlan *et al.*, *Lancet 337*:1304-1308 (1991) (cited in the Specification at page 91, lines 9-16).

Fourth, there is at least one additional example in the art of a chelator (clioquinol) that was first shown to be effective in solubilizing Aβ deposits *in vitro,* and was subsequently found to be effective in the treatment of Alzheimer's disease when administered to patients. (The parallels between the present invention and the results that were obtained with clioquinol are discussed in more detail below.)

In view of the foregoing, a person of ordinary skill in the art would have concluded that the *in vitro* results obtained with bathocuproine (and the other chelators described in the specification) are indicative of the results that would be achieved when the chelator is administered to a subject; *i.e.*, it is reasonable to conclude that the administration of bathocuproine to a subject would result in the treatment of amyloidosis. There has been no specific evidence presented to contradict the logic underlying this conclusion.

The Examiner has not presented any specific evidence to suggest that, even though bathocuproine solubilizes Aβ *in vitro*, this chelator would be ineffective in treating amyloidosis in a subject. The Examiner originally cited Fonte, Cuajungco and Gnjec as supporting the position that *in vitro* results with a metal chelator may not be indicative of *in vivo* results. *See* Office Action dated May 22, 2003, page 7, line 11, through page 8, line 11. (Appellants note that in the Advisory Action the Examiner stated that these references

were simply intended to indicate "the unpredictability of the state of the art." *See* Advisory Action at page 2, line 19). Regardless of which argument these references were cited to support, none of the references address the issue of whether *in vitro* results with a metal chelator are indicative of *in vivo* results. Therefore, no evidence has been presented to support the assertion that the *in vitro* results with bathocuproine are not indicative of the biological results that would be obtained when bathocuproine is administered to a subject.

The Examiner stated that "the *in vitro* results obtained with bathocuproine *may not necessarily be indicative* of the results obtained with this metal chelator *in vivo*." Office Action dated May 22, 2003, page 7, lines 11-12 (emphasis added). In other words, the Examiner has indicated that the enablement rejection would be maintained unless it is shown that the *in vitro* results with bathocuproine are "*necessarily . . . indicative*" of the results that would be obtained with bathocuproine *in vivo*. As mentioned previously, the Examiner has the initial burden of showing that the invention is *not* enabled. *See Marzocchi*, 439 F.2d at 224, 169 USPQ at 370 ("it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.") It is therefore legally improper for the Examiner to require proof that bathocuproine would *necessarily* treat amyloidosis in a subject when no specific evidence to the contrary has been presented.

Even though it is not Appellants' initial burden to establish that the invention is enabled, Appellants have nonetheless presented several lines of evidence to indicate that the *in vitro* results with bathocuproine reflect the results that would be obtained when this chelator is administered to a subject. *See* discussion set forth above. The Examiner has not

presented any evidence to suggest that this is not the case. Thus, a *prima facie* case of non-enablement has not been established.

(d) Clioquinol

As mentioned above, the metal chelator clioquinol has been shown to be effective in the treatment of Alzheimer's disease. *See* Ritchie *et al.*, "Metal complexation with iodochlorhydroxyquin (clioquinol) targeting Aβ amyloid deposition and toxicity in Alzheimer's disease: proof-of-concept and safety" (unpublished manuscript, submitted for publication) (2003) (copy attached hereto as Exhibit 6). Clioquinol, like bathocuproine, was first shown to promote the solubilization of Aβ *in vitro*. *See* Cherny *et al.*, *Neuron 30*:665-676 (2001) (copy attached hereto as Exhibit 7). The *in vitro* results with clioquinol provided the foundation for subsequent clinical work with this chelator.

The results with clioquinol support Appellants' position that the present invention is enabled in two respects. First, the clioquinol example shows that a chelator's ability to promote Aβ solubilization *in vitro* likely reflects its ability to treat conditions associated with Aβ deposition *in vivo*. Second, the results with clioquinol show that persons of ordinary skill in the art were able to successfully formulate and administer a metal chelator to subjects without undue experimentation. Since persons of ordinary skill in the art were able to successfully formulate and administer clioquinol using only routine methods, there is no reason to believe that persons of ordinary skill in the art could not have also been able to successfully formulate and administer bathocuproine. The Examiner has not provided any evidence or scientifically sound reasoning to indicate that there is a difference in the burden

on a person of ordinary skill in the art to formulate bathocuproine for administration to a subject as compared to the burden required to formulate and administer clioquinol.

The Examiner has not presented any evidence or scientifically sound reasoning to indicate that the success obtained with clioquinol would not have also been achieved with bathocuproine. The Examiner simply stated that clioquinol is specific for copper and zinc ions and has a different chemical make-up and structure than bathocuproine, which is specific for copper. *See* Office Action dated May 22, 2003, page 9, lines 12-16. The Examiner has not explained why such differences at the chemical level make it unlikely that bathocuproine would exert therapeutic effects when administered to a subject. Regardless of whether clioquinol differs from bathocuproine at the chemical level, the fact remains that persons of ordinary skill in the art were clearly able to formulate and administer metal chelators to subjects for therapeutic purposes without undue experimentation.

Finally, the Examiner's arguments relating to whether the results with clioquinol suggest similar results with bathocuproine (as well as the arguments relating to whether the *in vitro* results with bathocuproine are indicative of *in vivo* results with this chelator) are tangential to the basic inquiry in a proper enablement analysis. That is, the Examiner's arguments are aimed at rebutting Appellants' assertions that the invention *is* enabled. The Examiner, however, has not demonstrated that making and using the claimed invention would have required undue experimentation. The Examiner's position is that Appellants have not proven that the results with clioquinol reflect similar results that would be obtained with bathocuproine. According to the Examiner, "[b]athocuproine *may* have different physiological effects after administration to a subject than does clioquinol." Office Action dated May 22, 2003, page 9, lines 15-16, emphasis added. Such arguments, however, do not

satisfy the Examiner's initial burden of showing that the claimed invention is *not* enabled. Since it is not Appellants' initial burden to prove that the invention *is* enabled, a *prima facie* case of non-enablement cannot be established by arguing that Appellant's have not definitively proven enablement. Therefore, the Examiner's arguments as to whether the results with clioquinol reflect the results that would be obtained with bathocuproine cannot support a *prima facie* case of non-enablement.

D. Summary

A person of ordinary skill in the art would have been able to make and use the subject matter encompassed by the present claims without undue experimentation. The specification provides specific guidance regarding the formulation and administration of bathocuproine (and bathocuproine/indomethacin) in order to treat amyloidosis in a subject. In addition to the teachings in the specification, a skilled artisan would have been guided by the knowledge in the art relating to the formulation and administration of pharmaceutical compositions for therapeutic purposes. The examples in the specification along with other evidence in the art (*e.g.*, the results obtained with clioquinol) strongly indicate that bathocuproine would be successful in treating amyloidosis in a subject.

No specific evidence has been presented to suggest that the claimed invention is not enabled. The arguments that have been presented do not address the primary issue of whether or not a skilled person in the art would have been able to make and/or use the subject matter of the present claims without undue experimentation. In essence, the Examiner's argument is that Appellants have failed to definitively prove that the invention would function as intended, *i.e.*, that bathocuproine would -- without question -- treat

amyloidosis when administered to a subject. Appellants believe that substantial evidence has been presented to indicate that the invention would function as intended. Moreover, under 35 U.S.C. § 112, first paragraph, argumentation as to whether an Applicant has proven that the invention *is enabled* cannot substitute for the Examiner's primary responsibility of presenting particular evidence that the invention is *not enabled.* Thus, the Examiner's arguments are legally insufficient to establish a *prima facie* case of non-enablement.

In view of the foregoing remarks, Appellants respectfully request that the Board reverse the Examiner's § 112, first paragraph rejection of claims 1, 2 and 37 and remand this application for issue.

Respectfully submitted,

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IX. Appendix (37 C.F.R. § 1.192(c)(9))

1. A method of treating amyloidosis in a subject, said method comprising administering to said subject an effective amount of (a) bathocuproine or a hydrophobic derivative thereof; and (b) one or more pharmaceutically acceptable carriers or diluents; for a time and under conditions to bring about said treatment; and

wherein said bathocuproine or hydrophobic derivative thereof reduces, inhibits or otherwise interferes with amyloid beta peptide (Aβ)-mediated production of radical oxygen species.

2. The method of claim 1 further comprising administering to the subject an effective amount of indomethacin, or a pharmaceutically acceptable salt thereof.

37. A pharmaceutical composition for treatment of conditions caused by amyloidosis, amyloid beta peptide (Aβ)-mediated reactive oxygen species (ROS) formation, or both, comprising: (a) bathocuproine or a hydrophobic derivative thereof; (b) indomethacin or a hydrophobic derivative thereof; and (c) one or more pharmaceutically acceptable carriers or diluents.